Predictors of the response to treatment in anemic hemodialysis patients with high serum ferritin and low transferrin saturation

AK Singh[1], DW Coyne[2], W Shapiro[3] and AR Rizkala[4], the DRIVE Study Group

[1]Renal Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA; [2]Department of Medicine, Washington University School of Medicine, St Louis, Missouri, USA; [3]Brookdale Physicians Dialysis Center, Brooklyn, New York, USA and [4]Clinical Affairs, Watson Laboratories, Inc., Morristown, New Jersey, USA

Treating hemodialysis patients to combat anemia corrects hemoglobin but exacerbates iron deficiency by utilizing iron stores. Patients needing iron should receive this by intravenous (i.v.) means. The Dialysis patients' Response to IV iron with Elevated ferritin (DRIVE) trial investigated the role of i.v. iron in anemic patients with high ferritin, low transferrin saturation, and adequate epoetin doses. We examined whether baseline iron and inflammation markers predict the response of hemoglobin to treatment. Patients (134) were randomized to no added iron or to i.v. ferric gluconate for eight consecutive hemodialysis sessions spanning 6 weeks with epoetin increased by 25% in both groups. The patients started with hemoglobin less than or equal to 11 g/dl, ferritin between 500 and 1200 ng/ml, and transferrin saturation of less than 25%. Significantly, patients with a reticulocyte hemoglobin content greater than or equal to 31.2 pg were over five times more likely to achieve a clinically significant increase in hemoglobin of greater than 2 g/dl. Lower reticulocyte hemoglobin contents did not preclude a response to i.v. iron. Significantly higher transferrin saturation or lower C-reactive protein but not ferritin or soluble transferrin receptor levels predicted a greater response; however their influence was not clinically significant in either group. We conclude that none of the studied markers is a good predictor of response to anemia treatment in this patient sub-population.

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Correspondence: *AK Singh, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Email: asingh@partners.org*

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Anemia treatment in the hemodialysis population with erythropoiesis-stimulating agents increases hemoglobin but consumes iron stores, frequently resulting in iron deficiency. Blood loss in the dialysis circuit, laboratory testing, interventional procedures, and gastrointestinal bleeding lead to continuing iron losses.[1] Oral iron therapy is usually ineffective in providing sufficient iron in this population.[1,2] Consequently, the National Kidney Foundation-Kidney Disease Outcome Initiative (NKF-KDOQI) strongly recommends that hemodialysis patients needing iron should be treated with intravenous (i.v.) iron therapy.[1–3]

Serum ferritin and transferrin saturation (TSAT) are routinely utilized in dialysis patients to aid in diagnosing iron deficiency and in guiding iron therapy. Uniformly low TSAT ($<20\%$) and ferritin (<200 ng/ml) are clear indicators of iron deficiency and predict a higher likelihood of response to i.v. iron.[1] When TSAT and ferritin are both elevated, that is, TSAT $>20\%$ and ferritin >200 ng/ml, adequate iron stores are likely present and the likelihood of response to iron is low. However, ferritin and TSAT values are frequently discordant, as they are, respectively, positive and negative acute phase reactants.[4] Consequently, in the setting of inflammation or malnutrition, simultaneously high ferritin and low TSAT are frequently encountered and difficult to evaluate.[1,2]

Ideally, other tests could predict responsiveness to i.v. iron. Studies in hemodialysis patients have repeatedly found TSAT and ferritin as poor predictors of hemoglobin responsiveness to i.v. iron.[5–9] However, these studies have several limitations, including enrolling limited numbers of patients with ferritin values >500 ng/ml and lack of adequate control groups.[4] The 2006 KDOQI Anemia guidelines noted a lack of sufficient evidence of responsiveness to iron when ferritin is >500 ng/ml, and stated 'routine administration' could not be recommended.[1] Additionally, the guidelines recommended use of reticulocyte hemoglobin content (CHr) <29 pg/cell as an indicator of iron deficiency.[1] When evaluating iron needs in patients with ferritin >500 ng/ml, factors such as erythropoiesis-stimulating agents dose,

clinical status, TSAT values, and hemoglobin trends should be taken into account.[1]

Since release of the 2006 KDOQI anemia guidelines, the Dialysis Patients' Response to i.v. iron with Elevated ferritin (DRIVE) study has demonstrated that ferric gluconate was superior to no iron in improving hemoglobin levels in anemic hemodialysis patients with ferritin of 500–1200 ng/ml and TSAT $\leqslant$25%.[10] By week 6, patients receiving 1 g of ferric gluconate in addition to a 25% increase in epoetin dose experienced a mean hemoglobin change of 1.6 g/dl compared with only 1.1 g/dl in patients receiving a 25% increase in epoetin dose alone. In addition, the ferric gluconate patients mounted a clinically significant hemoglobin response more frequently and more quickly than the no iron patients. The amount of i.v. iron received by either patient group in the 4 weeks before enrollment had no impact on hemoglobin change.[10] Further, in the observational extension study of DRIVE, also known as DRIVE-II, hemoglobin changes were sustained until at least week 12 from the start of therapy despite significantly lower epoetin doses in the patients randomized to ferric gluconate (Kapoian *et al. J Am Soc Nephrol* 2006; **17**: 479A).

In this report we explore the value of ferritin, TSAT, CHr, C-reactive protein (CRP), and soluble transferrin receptor (sTfR) as predictors of iron responsiveness based on the DRIVE study data, which were pre-specified objectives of that trial. We also investigated the effect of increasing epoetin doses on responsiveness, an important treatment component that has not been studied previously.

RESULTS

Of the 134 randomized patients, 129 were included in the intent-to-treat (ITT) population (no iron $n=65$, i.v. iron $n=64$).[10] Of those 129 patients, 93 were included in the per-protocol (PP) population (no iron $n=50$, i.v. iron $n=43$). Baseline demographic and laboratory characteristics were similar in the two groups in both the ITT and PP populations (Table 1). Of note, >80% of the patients had a baseline CHr >29 pg/cell, the target CHr level recommended by the 2006 KDOQI clinical practice recommendations.[1] Changes in homocysteine levels were similar in the two groups (median change; i.v. iron 0.5 μmol/L vs no iron −1.7 μmol/L, $P=0.598$).

We attempted to explore the underlying reason why patients had a baseline ferritin at or above vs below the

Table 1 | Baseline characteristics by treatment group and analysis population

	ITT population		PP population[a]	
Parameter	No iron (*N*=65)	i.v. iron (*N*=64)	No iron (*N*=50)	i.v. iron (*N*=43)
Age (years)	58.7±15.2	61.2±13.0	59.1±14.9	60.3±12.6
Females (*n* (%))	37 (56.9)	27 (42.2)	29 (58.0)	21 (48.8)
Weight (kg)	75.0±22.3	76.4±21.0	77.6±23.0	71.2±13.8
Height (cm)	168.1±9.8	171.9±36.1	168.9±9.9	165.1±9.6
Race, n (%)				
White	20 (30.8)	20 (31.3)	17 (34.0)	13 (30.2)
African American	33 (50.8)	30 (46.9)	26 (52.0)	20 (46.5)
Hispanic	9 (13.8)	9 (14.1)	6 (12.0)	6 (14.0)
Asian/Pacific Islander	2 (3.1)	5 (7.8)	1 (2.0)	4 (9.3)
Other	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hemodialysis access, n (%)				
AV fistula	30 (46.2)	33 (51.6)	26 (52.0)	20 (46.5)
AV graft	21 (32.3)	20 (31.3)	14 (28.0)	15 (34.9)
Temporary catheter	3 (4.6)	2 (3.1)	2 (4.0)	1 (2.3)
Permanent catheter	11 (16.9)	9 (14.1)	8 (16.0)	7 (16.3)
i.v. iron in previous 4 weeks, *n* (%)	24 (36.9)	22 (34.4)	21 (42.0)	13 (30.2)
i.v. iron given in previous 4 weeks (mg)	70±108	61±103	79.5±113.4	41.9±69.2
Homocysteine (μmol/l)	27.3±9.8	25.4±8.2	27.8±9.1	25.0±6.9
Most recent Kt/*V*	1.7±0.3	1.6±0.4	1.7±0.3	1.7±0.4
Hemoglobin (g/dl)	10.2±0.7	10.4±0.8	10.2±0.7	10.4±0.8
TSAT (%)	19.0±4.1	18.2±4.2	19.3±3.9	18.0±4.4
Serum ferritin (ng/ml)	765±193	759±190	768±182	772±200
CHr (pg/cell)	31.0±2.8	31.4±2.7	31.2±2.8	31.9±2.7
CHr>29 pg/cell, *n* (%)	54 (83.1)	51 (79.7)	43 (86.0)	36 (83.7)
sTfr (mg/l)	6.1±2.2	6.2±2.5	5.9±2.3	6.3±2.6
C-reactive protein (mg/l)[b]	25.5±29.3	29.3±39.2	22.0±23.1	25.5±34.5
Epoetin dose (IU/kg/week)	495±272	448±229	444±234	452±227

CHr, reticulocyte hemoglobin content; ITT, intent-to-treat; PP, per-protocol; TSAT, transferrin saturation; sTfr, soluble transferrin receptor.
Continuous variables are summarized using mean±s.d.
[a]More i.v. iron patients than no iron patients were excluded from the PP population because they had to satisfy one more criterion to be in the PP population (receiving the entire 1 g of i.v. ferric gluconate).
[b]C-reactive protein values were obtained using the high-sensitivity assay.

median (true iron stores or inflammation) by tabulating the number of patients who had TSAT, CHr, CRP, or albumin at/above vs. below the respective median and by dividing patients according to the degree of response. We did not observe any significant differences (data not shown).

The proportions of patients achieving hemoglobin increases >1 g/dl in any 2-week period were 40.9 and 43.9% in the no iron and the i.v. iron groups, respectively ($P=0.725$). Regardless of treatment arm, those with baseline CRP <14.1 mg/l were 3.3 times more likely to experience this rate of increase ($P=0.001$).

Hemoglobin change and baseline values of response markers

Table 2 summarizes the impact of one unit change in TSAT, ferritin, CHr, sTfR, CRP, and epoetin dose increase (referred to henceforth as response markers) on hemoglobin change from baseline to week 6 while controlling for the i.v. iron treatment effect and baseline hemoglobin values. Table 2 also summarizes how i.v. iron impacted hemoglobin change when adjusting for each of the studied response markers.

In the ITT population, while TSAT, CRP, and epoetin dose increase influenced hemoglobin change regardless of treatment (TSAT, $P=0.025$; CRP, $P=0.006$; epoetin dose, $P=0.001$), only epoetin dose increase resulted in a clinically significant change in hemoglobin levels. For every 1% increase in baseline TSAT, hemoglobin increased by only 0.06 g/dl (95% confidence interval (CI) = 0.01–0.12 g/dl). Every 1 mg/l increase in baseline CRP predicted a change of only −0.01 g/dl in hemoglobin at week 6 (95% CI = −0.02, −0.00 g/dl). In contrast, each 1 IU/kg/week increase in baseline epoetin dose predicted an increase of 0.006 g/dl in hemoglobin (95% CI = 0.001–0.010). Considering that the mean baseline epoetin dose in the study was ~500 IU/kg/week (Table 1) and that the protocol mandated a 25% increase for all patients, the resulting increase of 125 IU/kg/week effectively enhanced the rise of hemoglobin from baseline by ~0.8 g/dl, independent of study treatment. The PP analysis confirmed the same findings for CRP and epoetin dose increase only. Baseline serum ferritin, CHr, and sTfR had no statistically significant effect on hemoglobin change at week 6 in both the ITT and the PP analyses.

In both analysis populations, administration of 1 g of ferric gluconate to the i.v. iron group predicted greater hemoglobin change at week 6 by 0.5–0.7 g/dl ($P<0.05$) regardless of the baseline value of any of the response markers including epoetin dose increase (Table 2). Baseline homocysteine levels had no impact on hemoglobin change ($P>0.4$ in both analysis populations). In virtually all the models, a 1 g/dl decrease in baseline hemoglobin values was associated with 0.3–0.7 g/dl increase in hemoglobin at week 6 ($P<0.05$).

Hemoglobin increase ⩾2 g/dl and baseline values of response markers

Figure 1a–f and Figure 2a–f summarize the odds ratios (ORs) of achieving a hemoglobin response (⩾2g/dl increase) if patients had baseline values at/above vs. below the median of each response marker in the no iron and i.v. iron groups, respectively. Values below the median were the reference category. Table 3 summarizes the sensitivity and specificity of using median response markers' baseline values in predicting hemoglobin response ⩾2g/dl.

Table 2 | Impact of one unit change in each response marker and use of i.v. iron on change in hemoglobin[a]

		Intent-to-treat population (*N*=129)		Per-protocol population (*N*=93)	
Response marker	Model Parameter	Coefficient (95% CI)[b]	*P*-value	Coefficient (95% CI)[b]	*P*-value
TSAT	Baseline TSAT	0.06 (0.01–0.12)	0.025	0.03 (−0.04–0.09)	0.404
	Receiving i.v. iron	0.59 (0.12–1.0)	0.013	0.69 (0.18–1.21)	0.009
Ferritin	Baseline ferritin	0.000 (−0.001–0.001)	0.721	−0.000 (−0.002–0.001)	0.712
	Receiving i.v. iron	0.52 (0.06–0.99)	0.028	0.66 (0.15–1.17)	0.012
CHr	Baseline CHr	0.07 (−0.02–0.15)	0.131	0.08 (−0.02–0.17)	0.101
	Receiving i.v. iron	0.51 (0.05–0.98)	0.032	0.62 (0.11–1.13)	0.018
sTfR	Baseline sTfR	0.07 (−0.03–0.17)	0.175	0.08 (−0.02–0.19)	0.110
	Receiving i.v. iron	0.50 (0.04–0.97)	0.035	0.60 (0.09–1.11)	0.022
CRP	Baseline CRP	−0.01 (−0.02– −0.00)	0.006	−0.01 (−0.02– −0.00)	0.008
	Receiving i.v. iron	0.58 (0.12–1.0)	0.014	0.71 (0.22–1.20)	0.005
Epoetin	Increase in dose[a]	0.006 (0.003–0.010)[c]	0.001	0.005 (0.000–0.009)	0.045
	Receiving i.v. iron	0.5 (0.1–1.00)	0.017	0.6 (0.1–1.1)	0.018

95% CI, 95% confidence interval; TSAT, transferrin saturation; CHr, reticulocyte hemoglobin content; sTfR, soluble transferrin receptor; CRP, C-reactive protein.
This table presents results of separate multiple regression models, one for each examined response marker. Each model included baseline hemoglobin, value of the response marker being examined, and treatment arm (i.v. iron; yes/no).
[a]Examples of one unit changes: TSAT, from 18 to 19%; ferritin, from 550 to 551; CHr from 30 to 31 pg/cell; sTfR, from 5 to 6 mg/L; CRP, from 15 to 16 mg/l; Epoetin, from 75 to 76 IU/kg/week.
[b]The response marker coefficient is the magnitude of change in hemoglobin at week 6 that is associated with one unit change in the baseline value of the response marker. I.v. iron coefficient is the difference between administration of i.v. iron in the form of ferric gluconate and administration of no iron.
[c]Magnitude of increase in epoetin dose is in IU/kg/week, which is approximately 25% greater than the baseline dose given before the study started.

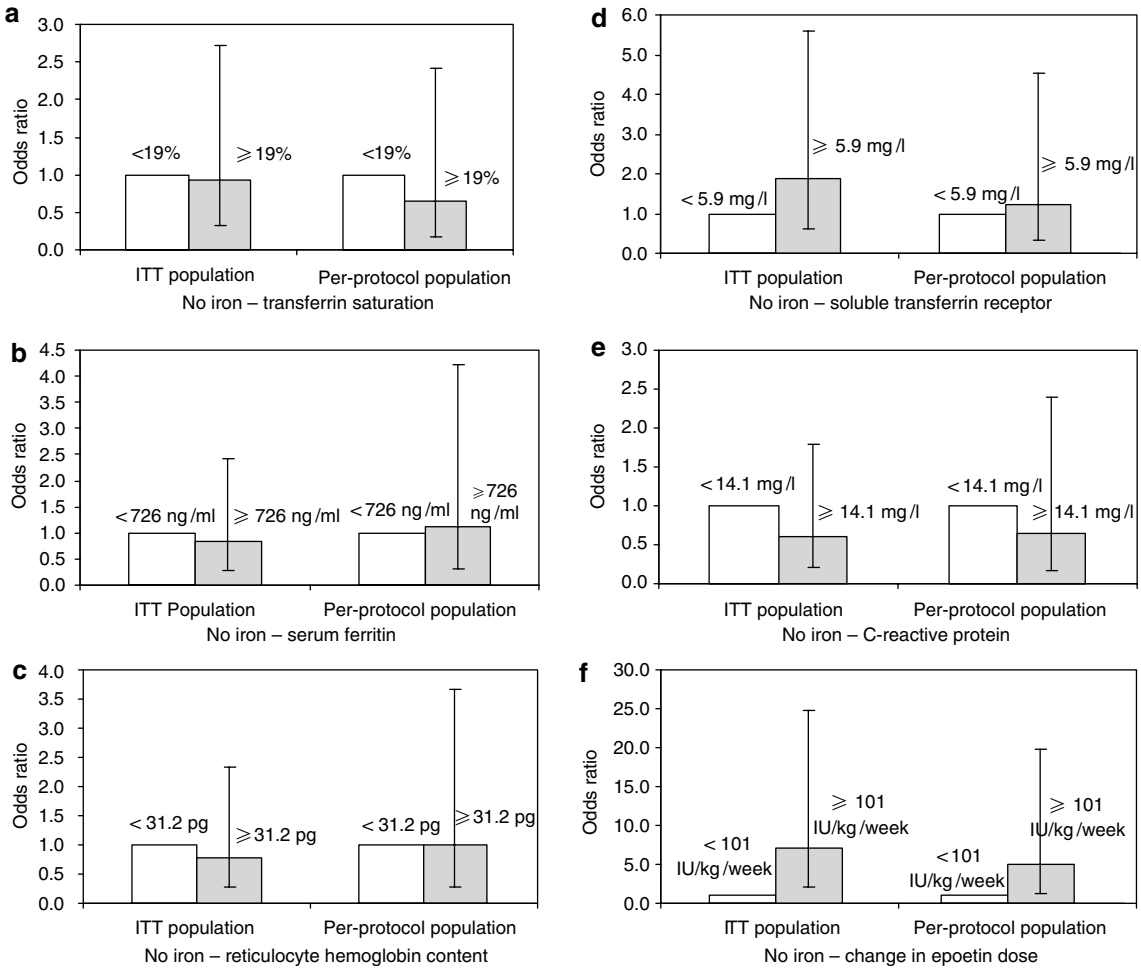

Figure 1 | Likelihood of response to anemia treatment without i.v. iron. (**a**–**f**) Ability of (**a**) transferrin saturation, (**b**) serum ferritin, (**c**) reticulocyte hemoglobin content, (**d**) soluble transferrin receptor, (**e**) C-reactive protein, and (**f**) magnitude of epoetin dose increase to predict likelihood of a clinically significant hemoglobin response (⩾2 g/dl increase in hemoglobin) to anemia treatment without the use of iron. (**f**) Response appears to be primarily driven by the magnitude of epoetin dose increase ($P<0.05$).

Predictors of response in the no iron group

Within the no iron group (25% epoetin dose increase alone), none of the response markers other than absolute value of epoetin dose increase predicted a statistically and clinically significant response to treatment. Despite all patients having received a 25% increase in their baseline epoetin dose, patients receiving ⩾101 IU/kg/week increase in their baseline epoetin dose were ~7.03 times (95% CI = 2.00–24.76) more likely to achieve a hemoglobin response ⩾2 g/dl than those receiving less (Figure 1f). A similar trend was noted in the PP population. However, using a ⩾101 IU/kg/week epoetin increase as a predictor of response lacked adequate sensitivity (48.4%) despite good specificity (88.2%; Table 3).

Predictors of response in the i.v. iron group

In the i.v. iron group, a higher baseline CHr (Figure 2c) and a lower baseline CRP (Figure 2e) predicted greater likelihood of response (Table 2). In the ITT population, the OR of achieving ⩾2 g/dl hemoglobin response in patients with baseline CHr ⩾31.2 pg/cell relative to those with lower values was 5.3 (95% CI = 1.78–15.83). As noted in Table 3, using a CHr level cutoff of ⩾31.2 pg/cell to predict hemoglobin response had acceptable specificity (75.0%), but mediocre sensitivity (63.9%). This trend was also observed in the PP analysis.

In the ITT analysis, CRP ⩾14.1 mg/l was associated with a significantly lower likelihood of response (OR 0.36, 95% CI = 0.13–0.99). Only a trend was observed in the PP analysis. We performed a multivariate logistic regression analysis comparing i.v. iron with no iron while controlling for CRP category. Regardless of baseline CRP category, patients receiving i.v. iron were more likely to achieve a hemoglobin response ⩾2 g/dl than no iron patients (OR 2.18, 95% CI = 1.04–4.57). Sensitivity and specificity of using a cutoff value ⩽14.0 mg/l did not predict response (Table 3).

DISCUSSION

The DRIVE study assessed the efficacy of i.v. iron in dialysis patients with elevated ferritin and low TSAT receiving epoetin doses ⩾22 500 IU/week.[10] In this report we explored the

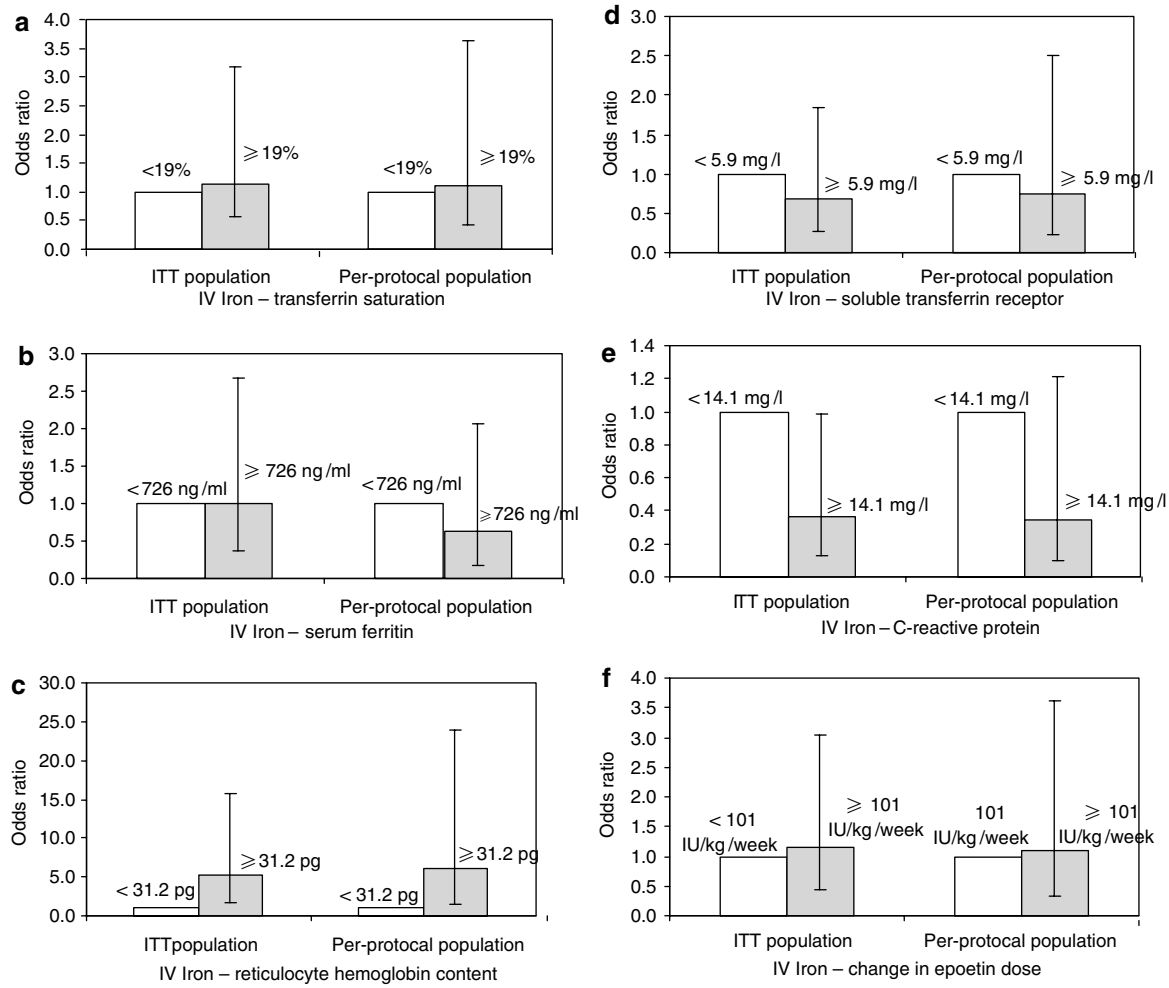

Figure 2 | Likelihood of response to anemia treatment using i.v. iron. (**a**–**f**) Ability of (**a**) transferrin saturation, (**b**) serum ferritin, (**c**) reticulocyte hemoglobin content, (**d**) soluble transferrin receptor, (**e**) C-reactive protein, and (**f**) magnitude of epoetin dose increase to predict likelihood of a clinically significant hemoglobin response (⩾2 g/dl increase in hemoglobin) to 1 g of i.v. iron (8 × 125 mg ferric gluconate). (**c**) Reticulocyte hemoglobin content ⩾31.2 pg/cell and (**e**) C-reactive protein <14.1 mg/l were associated with greater likelihood of response to i.v. iron (both $P<0.05$). However, the likelihood of response to anemia treatment with i.v. iron was always greater than without i.v. iron, regardless of any level of reticulocyte hemoglobin content, C-reactive protein, or any other analyte.

Table 3 | Discriminative properties of response to assigned treatment based on the intent-to-treat analysis

	No iron		i.v. iron	
Response marker and value	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
Baseline TSAT ⩾ 19%	28.6	70.0	48.5	54.8
Baseline ferritin ⩾ 726 ng/ml	27.3	68.8	46.9	53.1
Baseline CHr ⩾ 31.2 pg/cell	26.7	68.6	63.9	75.0
Baseline sTfr ⩾ 5.9 mg/l	35.3	77.4	42.4	48.4
Baseline CRP ⩽ 14.0 mg/l	34.4	75.8	59.4	65.6
Increase in epoetin dose ⩾ 101 IU/kg/week	48.4	88.2	48.5	54.8

CHr, reticulocyte hemoglobin content; sTfR, soluble transferrin receptor; TSAT, transferrin saturation.

value of several parameters of iron status and inflammation in predicting response to i.v. iron. We observed that in patients being treated with i.v. iron, baseline CHr ⩾ 31.2 pg/cell strongly predicted the likelihood of achieving a clinically important hemoglobin response compared with lower levels. Higher CRP levels decreased the extent and likelihood of mounting a response to i.v. iron, but did not exclude it. Furthermore, we found that TSAT, ferritin, sTfR, and increasing epoetin doses are poor predictors of response to i.v. iron.

Unlike i.v. iron-treated patients, clinically significant hemoglobin response in patients not receiving iron is

influenced almost exclusively by the absolute magnitude of epoetin dose increase. Although all patients received the 25% increase in epoetin dose recommended by the KDOQI guidelines,[1–3] those receiving ⩾101 IU/kg/week increase were much more likely to mount a clinically significant hemoglobin response. This emphasizes the fact that the 25% epoetin dose increase recommended by the KDOQI guidelines, although reasonable, appears inadequate for the treatment of all patients with ferritin of 500–1200 ng/ml, TSAT ⩽25%, and baseline epoetin doses ⩾225 IU/kg/week or ⩾22 500 IU/week. Although C-reactive protein has a statistically significant impact on hemoglobin change, the impact does not appear to be clinically meaningful (Figure 1e). Regardless of baseline values of TSAT, ferritin, CHr, sTfR, or CRP or magnitude of epoetin dose increase, i.v. ferric gluconate given to the i.v. iron group consistently results in a greater hemoglobin response than giving no iron.

We chose a 2 g/dl increase in hemoglobin as a clinically significant response because all patients received a 25% increase in epoetin dose at the start and were expected to experience ⩾1 g/dl increase during the study. Thus, a stricter definition of response was warranted to detect a separation between groups and to better identify the i.v. iron effect.[10] Therefore, we believe that our results would have been similar had we maintained the epoetin dose unchanged for 6 weeks and randomized patients to 1 g of i.v. ferric gluconate vs. no iron. The latter hypothetical study design was not possible because many nephrologists felt it would be unethical to deny patients the current recommendation by NKF K-DOQI of a 25% increase in epoetin dose.[2,3,10]

The results of ferritin and TSAT tests have long guided the decision of whether to administer iron therapy to hemodialysis patients. These tests are simply interpreted when concordant. Unfortunately, the presence of inflammation frequently compromises their ability to assess actual iron status.[11] High ferritin and low TSAT are commonly observed in dialysis patients in clinical practice, and can usually be explained by accompanying inflammation. Several studies have attempted to investigate the ability of TSAT and serum ferritin to differentiate between responders and non-responders to i.v. iron.[5–9] Although these studies were smaller than ours reported herein, contained very few or no patients with baseline ferritin ⩾500 ng/ml, and did not include a control arm, they invariably observed that the TSAT and ferritin did not predict response to i.v. iron.[4] Our results in patients with ferritin ⩾500 ng/ml, TSAT ⩽25%, and apparently adequate epoetin doses (mean baseline dose 450–500 IU/kg/week) confirm those previous findings. Indeed, despite a belief held by some that when ferritin levels exceed 500 ng/ml iron stores are adequate and further i.v. iron administration is likely to be ineffective,[12,13] the primary finding of DRIVE is that, in the setting of an increase in epoetin dose, giving 1 g of ferric gluconate i.v. to this patient population is more effective in improving hemoglobin levels than not giving iron.[10] Although DRIVE answers neither the question of iron store adequacy in patients with ferritin of 500–1200 ng/ml and TSAT ⩽25% nor the long-term patient outcomes of such intervention, it demonstrates that these patients do benefit from a course of i.v. iron insofar as resulting in an improvement in iron parameters and in increasing hemoglobin in a clinically significant manner. However, neither TSAT nor ferritin provided sufficient discriminative value for clinical use. The response was similar in patients with baseline ferritin above or below 800 ng/ml.[10] The response was also similar when TSAT was above or below the median of 19%.[10]

It has been suggested that sTfR is a sensitive indicator of functional iron deficiency[14] and a useful predictor of hemoglobin response.[15] However, it has been shown that this marker offers no advantage over TSAT and ferritin in identifying patients who would benefit from additional i.v. iron treatments.[16] Although sTfR levels are increased in the setting of iron deficiency, they are also elevated as a result of increased erythropoiesis induced by epoetin, thereby masking the net effect of iron stores on this indicator.[17] This may have contributed to the failure of this marker to predict hemoglobin response in this study. Given the high cost of the sTfR assay (approximately US$125 per test) and its poor discriminative properties, we do not recommend using it in guiding i.v. iron therapy in this patient population.

The 2006 KDOQI anemia clinical practice recommendations[1] advocate a target CHr level >29 pg/cell based on two randomized controlled trials.[18,19] Fishbane *et al.*,[18] randomized hemodialysis patients to receive i.v. iron based on CHr or TSAT and ferritin criteria. In those receiving i.v. iron when CHr dropped below 29 pg/cell, cost of anemia treatment and cumulative i.v. iron administered was less than patients randomized to receive i.v. iron based on TSAT <20% or ferritin <100 ng/ml. The two groups had similar hematocrit levels and epoetin doses at study end. Kaneko *et al.*[19] randomized hemodialysis patients to receive i.v. iron when their CHr dropped below 32.5 pg/cell or when TSAT fell below 20%.There was no difference between the two groups in hematocrit or epoetin dose change, but only the group treated based on TSAT experienced a significant epoetin dose decrease. Although not specifically pointed out by the 2006 KDOQI clinical practice recommendations, patients in both studies (as well as studies investigating CHr's ability to identify responders to i.v. iron[20,21]) predominantly had baseline ferritin levels <500 ng/ml. Consequently, results from these two studies should be interpreted with caution insofar as extrapolating them to patients with higher ferritin levels. Although DRIVE did not target a specific CHr level by design, it provides some insights into the relationship between CHr levels and responsiveness to i.v. iron in patients with ferritin of 500–1200 mg/ml, TSAT ⩽25%, and adequate epoetin dose. In such patients, CHr levels ⩾31.2 pg/cell are associated with greater response than lower levels. Owing to fundamental design differences, our results cannot clearly be compared with prior studies.

As shown in Table 1, >80% of patients with ferritin of 500–1200 ng/ml and TSAT ⩽25% in DRIVE had a CHr

>29 pg/cell, that is, only <20% had a CHr <29pg/cell. However, ~47% of i.v. iron patients compared with only about 29% of the no iron patients had a clinically significant response.[10] Had the KDOQI clinical practice recommendations' CHr cutoff target value been correct for this patient population, we would have expected only about 20% of patients to respond. This shows that the >29 pg/cell CHr cutoff value is exceedingly low and does not apply to this population of hemodialysis patients. Interestingly, this population is precisely the one that clinicians often have trouble treating, causing them to resort to other iron bioavailability indices, like CHr, to guide their iron management decisions. Using the KDOQI recommended CHr cutoff may lead clinicians to withhold i.v. iron from patients who are very likely to benefit from it. Nevertheless, the sensitivity and specificity of the ⩾31.2 pg/cell CHr cutoff value were only 63.9 and 75.0%, respectively. Because these discriminative properties are modest at best, and because the only treatment known to raise CHr is to give i.v. iron, in light of our findings, we do not recommend the use of CHr in guiding i.v. iron administration decisions in this population.

It is unclear why higher rather than lower CHr levels were associated with greater likelihood of response to i.v. iron. One potential explanation is that patients with a low CHr have a magnitude of iron deficiency such that 1 g of iron is insufficient to generate a ⩾2g/dl increase in hemoglobin. Alternatively, the low CHr may reflect marked inability to mobilize iron from reticuloendothelial stores, resulting in a less efficient or delayed response to i.v. iron.

Our results suggest that inflammation, reflected by CRP levels, reduces the likelihood and extent of responding to i.v. iron, but does not exclude it. Compared with patients not receiving iron, patients receiving i.v. ferric gluconate were more than twice as likely to achieve a hemoglobin response ⩾2g/dl regardless of whether baseline CRP was above or below 14.1 mg/l. These results support the administration of a trial course of i.v. iron to patients with elevated CRP levels and hemoglobin ⩽11 g/dl despite adequate erythropoiesis-stimulating agents therapy.

This report is the first to investigate the use of magnitude of epoetin dose increases in predicting hemoglobin response in the clinical context of iron therapy. Despite the fact that all patients received a 25% increase in their baseline epoetin doses, those in the no iron group who received ⩾101 IU/kg/week were 4–7 times more likely to mount a ⩾2g/dl hemoglobin response than those who received smaller increases. In the i.v. iron group, likelihood of response was unaffected by the absolute epoetin dose increase. This suggests that patients with high ferritin and low TSAT on lower epoetin doses will also have a high response rate to i.v. iron therapy.

This analysis had potential limitations that merit discussion. The DRIVE study comprised of individuals with a high ferritin and low TSAT, receiving relatively high epoetin doses. Hence, conclusions regarding the validity of the various parameters of iron status and inflammation examined may not be generalizable to all hemodialysis patients. However, it is this patient group that is the most challenging to treat.[1,2] The very high OR for the association between CHr level and response to i.v. iron was associated with a wide confidence interval. A larger sample size would be required to narrow this confidence interval. The study did not measure the percent of hypochromic red cells as delays in measurement owing to shipping affect this test's results. This test has been reported to be an excellent predictor of iron responsiveness.[6,22] Further studies to evaluate percent of hypochromic red cells despite shipping delays may be warranted. We also did not measure hepcidin as no validated serum hepcidin assays were commercially available. Lastly, as we did not perform bone marrow biopsies to ascertain true iron stores, we were unable to generate any hypotheses regarding the underlying causes that drive ferritin to higher levels. However, others have reported that, in addition to predicting iron status, higher ferritin levels may result from a combination of inflammation and malnutrition in addition to iron stores.[23]

The US Food and Drug Administration-approved labeling for epoetin recommends that doses are decreased by 25% when the rate of hemoglobin rise exceeds 1 g/dl in a 2-week period.[24] We found that this dosing change threshold was achieved in approximately 42% of patients regardless of treatment assignment. Therefore, we recommend that patients of this sub-population who are given 25% epoetin dose increase alone or in combination with 1 g i.v. iron should be monitored closely so that appropriate dose adjustments are made, especially in those with CRP levels below 14.1 mg/l.

In conclusion, this study suggests efficacy for i.v. iron therapy among anemic hemodialysis patients with ferritin ⩽1200 ng/ml and TSAT ⩽25%. As continued i.v. iron use is targeted to replace iron losses,[2] our data do not support the current National Kidney Foundation-Kidney Disease Outcome Initiative suggestion of not treating patients with iron when their serum ferritin levels exceed 500ng/ml. Indeed, we suggest reconsideration of this recommendation. Our data suggest that no iron response parameter we measured warrants consideration in making an iron management decision. Although our finding, that higher CHr rather than lower CHr is associated with a greater likelihood of clinically important hemoglobin response to i.v. iron, is hypothesis-generating, our data suggest that CHr lacks adequate sensitivity and specificity to be used in guiding iron management decisions.

MATERIALS AND METHODS

The DRIVE study design and population were previously described.[10] Briefly, this study was an open-label, randomized, controlled, multicenter trial conducted in 37 centers across the United States. Eligible participants were maintenance hemodialysis patients ⩾18 years with hemoglobin ⩽11g/dl, TSAT ⩽25%, ferritin of 500–1200 ng/ml, baseline epoetin doses ⩾225 IU/kg/week or ⩾22 500 IU/week for ⩾2 weeks, and who received ⩽125 mg i.v.

iron per week during the 4 weeks preceding screening/baseline. Major exclusion criteria were significant blood loss within the prior 6 weeks, hematological disorders or malignancies, any active infection requiring systemic antibiotic therapy, and hospitalization within the 2 weeks before screening/baseline.

Patients were screened during week 0. Screening procedures included obtaining blood samples for hematology and serum chemistry assessments, including hemoglobin, TSAT, serum ferritin, sTfR, CHr, CRP, and homocysteine. If screening blood tests revealed TSAT $\leqslant$25%, ferritin 500–1200 ng/ml, and hemoglobin $\leqslant$11 g/dl, the patients were considered eligible for the study and their screening results were considered baseline values. Eligible patients were centrally randomized 1:1 to either no iron or to 1 g of ferric gluconate (Ferrlecit®, Watson Laboratories, Inc., Morristown, NJ, USA) administered in eight consecutive 125 mg doses beginning with the first hemodialysis session of week 1 (i.v. iron group). Baseline epoetin doses were raised by 25% in both groups starting with the first hemodialysis session of week 1, and then maintained for the entire study until the first hemodialysis session of week 6. Hemoglobin and CHr were obtained weekly before the second hemodialysis session throughout the 6-week study period.

All laboratory assessments were performed by a central laboratory. Serum iron and unsaturated iron binding capacity (UIBC), as well as the high sensitivity CRP, were obtained using the Olympus AU5400 analyzer (Olympus Diagnostics, Melville, NY, USA). Cobra Integra analyzer (Roche Diagnostics, Indianapolis, IN, USA) was used for sTfR levels. Advia 120 analyzer (Bayer Diagnostics) was used for CHr levels. Serum ferritin levels were obtained using the Advia Centeur analyzer (Bayer Diagnostics).

DRIVE was conducted in compliance with the Declaration of Helsinki, and approved by the human studies' committee at each center. All study participants provided informed consent before undergoing any study procedures. This trial was registered with the United States National Institutes of Health through the National Library of Medicine at http://clinicaltrials.gov/.

Analysis objectives

There were two objectives to this analysis. First, to investigate how baseline values of TSAT, serum ferritin, CHr, sTfR, and CRP and epoetin dose increases given during the study (response markers) impact change in hemoglobin levels from baseline to study end (week 6 or last available hemoglobin for those not completing the study) regardless of treatment assignment. Realizing that values of these response markers may have a statistically, but not clinically significant impact on hemoglobin changes, the other objective was to explore how these markers influence the likelihood of achieving a hemoglobin increase $\geqslant$2 g/dl to the assigned treatment. The rationale for choosing this definition of response was discussed previously.[10]

Statistical analyses

The primary predefined analysis was based on the ITT population, which included participants who received at least one study treatment and had at least one post-baseline hemoglobin value. A predefined confirmatory analysis was performed based on the PP population, which excluded participants who had any serious protocol deviations, received $<$75% of the scheduled epoetin doses, or $<$1000 mg of ferric gluconate (if randomized to i.v. iron).

The relationship between baseline response markers and hemoglobin change at week 6, that is, the first objective was analyzed using separate multiple linear regression models. Each model included baseline hemoglobin, value of the response marker being examined, and treatment arm (i.v. iron; yes/no). To achieve the second objective, baseline values of each response marker were grouped into two categories ($<$median value vs $\geqslant$median value). The relationship between hemoglobin response and response marker category was analyzed for each treatment arm separately using logistic regression. All statistical tests were conducted at $\alpha = 0.05$ significance level. All statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC, USA) or Stata 8.2 (StataCorp, College Station, TX, USA).

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REFERENCES

1. KDOQI Clinical Practice Guidelines and Clinical Practice. Recommendations for anemia in chronic kidney disease. *Am J Kidney Dis* 2006; **47**: S11–S145.
2. NKF-K/DOQI Clinical Practice. Guidelines for anemia of chronic kidney disease: update 2000. *Am J Kidney Dis* 2001; **37**: S182–S238.
3. NKF-DOQI Clinical Practice. Guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative. *Am J Kidney Dis* 1997; **30**: S192–S240.
4. Coyne DW. Iron indices: what do they really mean? *Kidney Int* 2006; **101**: S4–S8.
5. Mittman N, Sreedhara R, Mushnick R *et al.* Reticulocyte hemoglobin content predicts functional iron deficiency in hemodialysis patients receiving rHuEPO. *Am J Kidney Dis* 1997; **30**: 912–922.
6. Tessitore N, Solero GP, Lippi G *et al.* The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. *Nephrol Dial Transplant* 2001; **16**: 1416–1423.
7. Lin JL, Chang MY, Tan DT, Leu ML. Short-term small-dose intravenous iron trial to detect functional iron deficiency in dialysis patients. *Am J Nephrol* 2001; **21**: 91–97.
8. Fishbane S, Kowalski EA, Imbriano LJ, Maesaka JK. The evaluation of iron status in hemodialysis patients. *J Am Soc Nephrol* 1996; **7**: 2654–2657.
9. Low CL, Bailie GR, Eisele G. Sensitivity and specificity of transferrin saturation and serum ferritin as markers of iron status after intravenous iron dextran in hemodialysis patients. *Ren Fail* 1997; **19**: 781–788.
10. Coyne DW, Kapoian T, Suki W *et al.* Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the Dialysis Patients' Response to IV Iron with **E**levated Ferritin (DRIVE) Study. *J Am Soc Nephrol* 2007; **18**: 975–984.
11. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *New Engl J Med* 1999; **340**: 448–454.
12. Aronoff GR. Safety of intravenous iron in clinical practice: implications for anemia management protocols. *J Am Soc Nephrol* 2004; **15**: S99–S106.
13. Van Wyck DB, Bailie G, Aronoff G. Just the FAQs: frequently asked questions about iron and anemia in patients with chronic kidney disease. *Am J Kidney Dis* 2002; **39**: 426–432.
14. Daschner M, Mehls O, Schaefer F. Soluble transferrin receptor is correlated with erythropoietin sensitivity in dialysis patients. *Clin Nephrol* 1999; **52**: 246–252.
15. Ahluwalia N, Skikne BS, Savin V *et al.* Markers of masked iron deficiency and effectiveness of EPO therapy in chronic renal failure. *Am J Kidney Dis* 1997; **30**: 532–541.

16. Fusaro M, Munaretto G, Spinello M *et al.* Soluble transferrin receptors and reticulocyte hemoglobin concentration in the assessment of iron deficiency in hemodialysis patients. *J Nephrol* 2005; **18**: 72–79.
17. Chiang WC, Tsai TJ, Lin SL *et al.* Serum soluble transferrin receptor reflects erythropoiesis but not iron availability in erythropoietin-treated chronic hemodialysis patients. *Clin Nephrol* 2002; **58**: 363–369.
18. Fishbane S, Shapiro W, Dutka P, Valenzuela OF, Faubert J. A randomized trial of iron deficiency testing strategies in hemodialysis patients. *Kidney Int* 2001; **60**: 2406–2411.
19. Kaneko Y, Miyazaki S, Hirasawa Y *et al.* Transferrin saturation versus reticulocyte hemoglobin content for iron deficiency in Japanese hemodialysis patients. *Kidney Int* 2003; **63**: 1086–1093.
20. Fishbane S, Galgano C, Langley Jr RC, Canfield W, Maesaka JK. Reticulocyte hemoglobin content in the evaluation of iron status of hemodialysis patients. *Kidney Int* 1997; **52**: 217–222.
21. Bhandari S, Brownjohn A, Turney J. Effective utilization of erythropoietin with intravenous iron therapy. *J Clin Pharm Ther* 1998; **23**: 73–78.
22. Bovy C, Tsobo C, Capanzano L *et al.* Factors determining the percentage of hypochromic red blood cells in hemodialysis patients. *Kidney Int* 1999; **56**: 1113–1119.
23. Kalantar-Zadeh K, Rodriguez RA, Humphreys MH. Association between serum ferritin and measures of inflammation, nutrition and iron in haemodialysis patients. *Nephrol Dial Transplant* 2004; **19**: 141–149.
24. Amgen Inc. Epogen® (epoetin alfa) Prescribing Information. 19-Dec-2006.